does not reasonably provide enablement for polyomaviruses. The Examiner will note that Claim 42 has been amended to delete "polyomavirus." Thus, the rejection is obviated.

Claims 24-46 also stand rejected under §112, First Paragraph. The Examiner believes that Applicants' Specification, while enabling for in vitro uses of the stated viral constructs, does not provide enablement for in vivo gene therapy methods. To support the Examiner's position, the Examiner has provided a copy of the Orkin, et al. report on research in gene therapy, and has pointed out that the report describes only "antidotal claims of successful (gene) therapy." The report also states that "significant problems remain in all aspects of gene therapy." Implicit in the Examiner's views is that Applicants' invention, which claims certain viruses for ablating cancer cells, is gene therapy. Applicants respectfully disagree.

Support for Applicants' view that their invention is not gene therapy is provided in the form of a declaration under 35 U.S.C. §1.132 by Dr. Chris Maack, Onyx's Director of Regulatory Affairs and Clinical Operations. Dr. Maack declares that he sought guidance regarding the status of an Onyx virus representative of those described in Applicant's Specification from the Office of Recombinant DNA Activity of the National Institutes of Health prior to starting human clincial trials. Specifically he inquired whether the use of the virus would be considered gene therapy. If so, Onyx would have been required to get Recombinant DNA Advisory Committee (RAC) approval, or if not, Onyx would only have needed FDA approval. Dr. Maack in his declaration refers to two letters from Dr. Nelson A. Wibel, M.D., Director of the Office of Recombinant DNA Activity of the National Institutes of Health in which Dr. Wibel states unambiguously that Onyx-015, Onyx's adenovirus in clinical trials, does not have to be approved by RAC. In the letter dated August 16, 1995 he states that

the virus "does not meet the definition of recombinant DNA molecules, it is exempt from review on those grounds alone, and the consolidated review process established by the NIH and the FDA for human gene transfer protocols does not apply here. In conclusion, it appears that sole review by the FDA is appropriate for this circumstance." Thus, Applicants respectfully submit that since their invention is not gene therapy and that the Orkin et al. report, which the Examiner has cited to support a §112, First Paragraph rejection of the relevant claims, does not apply. Consequently, Applicants respectfully request that the rejection be withdrawn.

While Applicants believe that Orkin et al. is not an appropriate reference to base a §112, First Paragraph rejection, Applicants nevertheless wish to address the Examiner's remarks that the "Specification fails to disclose the intended patient, amounts of the viral vectors to be administered, what amount is considered to be therapeutically effective, the time course of administration, the sites of administration, the intended therapeutic product, the intended disease and the intended target organs." The Examiner also stated that the Specification lacks working examples, and concluded that it would require undo experimentation to practice Applicants' invention, as it relates to <u>in vivo</u> uses. Applicants disagree with the Examiner, and respectfully submit that little, if any, experimentation is required to practice Applicant's invention. The Examiner is referred to pages 27-31 of Applicant's Specification. There Applicants describe, in significant detail, methods and compositions for praticing the stated diagnostic and therapeutic applications of the invention. Applicants believe more than sufficient detail is described for a skilled practitioner of the art to practice the invention. For example, on page 28, lines 13-38 which bridge to page 29, lines 1-9, the Examiner will note that specific doses of virus (10^3-10^{12} virion particles per ml), as well as modes of administration (intravenous,

intraperitoneal, etc.), and target organs/disease (bronchogenic carcinoma, nasopharyngeal carcinoma, etc.) are provided.

Furthermore, although Applicants' invention is not gene therapy, Applicants wish to establish that it is enabled for in vivo killing of tumor cells, and to this end a declaration by Dr. Carla Heise is provided in which she declares that the invention E1A- mutant adenoviruses are effective in vivo against Rb- tumor cells. Dr. Heise's declaration should thus be sufficient to rebut the §112, First Paragraph lack of enablement rejection. Thus, the declaration forms a separate basis to traverse the §112, First Paragraph, rejection.

In summary Applicants submit that their invention is not gene therapy, and that little is required to practice the invention beyond injecting a desired virus over a range of concentrations into an appropriate tumor. Further, as stated by Dr. Heise, Applicants invention is enabled for in vivo applications. In this regard, Applicants draw the Examiner's attention to the standard for enablement set forth in In re Marzocchi et al., (CCPA 1971) 439 F2d, 169 USPQ 367. There the court held that § 112, first paragraph, requires nothing more than objective enablement. Applicants believe that their disclosure satisifies this standard considering the level of detail in the Specification and the ease with which the invention can be praticed.

In view of the above Amendments and Remarks, reconsideration of the claims is requested.

Enclosed is a PETITION FOR EXTENSION OF TIME UNDER 37 C.F.R. § 1.136 for extending the time to respond up to and including today, June 26, 1997.

The Commissioner is authorized to charge any underpayment or credit any overpayment to Deposit Account No. 15-0615 for any matter in

connection with this response, including any fee for extension of time, which may be required.

Respectfully submitted,

Date: June 26, 1997

By: _____
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